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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/919,298	07/31/2001	Joseph Edward Zahner	16850-8184	2484

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EXAMINER
WOITACH, JOSEPH T

ART UNIT	PAPER NUMBER
1632	14

DATE MAILED: 01/06/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

File

Office Action Summary

Application No.	Applicant(s)
09/919,298	Zahner et al.
Examiner	**Art Unit**
Joseph Woitach	1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Oct 15, 2002* .

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-9* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-9* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☒ The drawing(s) filed on *Jul 31, 2002* is/are a) ☒ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *5, 7, 10*
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

This application filed July 31, 2001, claims benefit to provisional application 60/254,551, filed December 12, 2000.

Applicants' pre-amendment filed February 20, 2002, paper number 8, has been received and entered. The specification has been amended. Applicants amendment filed October 15, 2002, paper number 13, has been received and entered. Claims 10-20 have been canceled. Claims 1-9 are pending and currently under examination.

Election/Restriction

Applicant's election without traverse of Group I, claims 1-9, in Paper No. 13, is acknowledged.

Information Disclosure Statement

With respect to the IDS submitted as papers number 6, 7 and 10, initialed and signed copies of the IDS forms are included with this action.

Additionally, it is noted that there the listing of references in the specification is not a proper information disclosure statement. See specification, pages 5-12. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be

submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-9 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (*Wands*, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (*Wands*, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or

absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case are discussed below.

The claims are broadly drawn to reprogramming any human somatic cell into a pluripotent stem cell by administering to said somatic cell an agent which promotes cellular reprogramming. Dependent claims recite specific agents which are known and used in the art to affect the methylation (5-aza-2'-deoxycytidine), acetylation (trichostatin A) and agents which affect the cell cycle (cyclin B). The specification provides a general outline for the basis of the invention, which is that during differentiation of a cell specific changes occur to the genome of the cell which destines the fate of a cell. The basis of the instant invention is to erase the changes which occur during differentiation, methylation patterns of the genome and acetylation of histones to restore the genome of a differentiated cell to a state which represents an undifferentiated stem cell. The specification provides a working example wherein an outer root sheath cell is removed, treated with trichostatin A, then treats the cells with the differentiating agent retinoic acid to demonstrate that the trichostatin A treatment was effective in undifferentiating the outer root cell. The working example demonstrates that outer root cell treated with retinoic acid take on a morphology which appears to be neuron-like, however this is based on morphology and no specific neuronal markers are demonstrated. Except for the

specific conditions set forth in the working examples, the specification provides no other specific conditions for the isolation or culturing conditions for other cell types.

As noted above, the agents specifically recited in the claims are known in the art and have been used extensively for studying specific effects of methylation and acetylation on gene regulation. The basis of the instant rejection focuses on the lack of specific guidance necessary to practice the instantly claimed method. More specifically, the instant invention is based on a concept which has been recognized in the art for determining the differentiation pathway of a cell, however the simplistic solution of applying an agent to a cell to reprogram a cell to become a totipotent stem cell with the specific agents contemplated is not supported by the art nor the specification.

At the time of filing, Kikyo *et al.* (J Cell Sci, 2000) review the state of the art for nuclear reprogramming. Kikyo *et al.* review many of the of the known changes which occur in the development of a cell from fertilization to adult including changes in methylation, acetylation, and HMG- histone exchange (see summary in figure 1). As acknowledged in the instant specification, Kikyo *et al.* teach that the only method known in the art for returning a nucleus of a somatic cell to a more pluripotent state is the use of nuclear transfer, the transfer of a somatic nucleus into an enucleated oocyte. Kikyo *et al.* teach that gene activation/deactivation during differentiation is a very complex process and probably determined by many factors. In summary of the art Kikyo *et al.* teach that affecting the somatic nucleus before nuclear transfer may provide a better nuclear donor, however such a simple approach is unlikely to resolve the

complex issues concerning the cell biology of the somatic cell nuclei (page 16, second column). Similar conclusions are made by Walsh *et al.* (IDS BQ) who provide a review of the nature of differentiation as it is related to methylation of several genes known to alter expression in a tissue specific pattern (pages 26-27). Walsh *et al.* teach that the methylation-development hypothesis has been put forward however the data that supports this hypothesis is ambiguous (page 31, first column). Walsh *et al.* conclude based on previous results in the art and on their new evidence that methylation plays only a minor role in mammalian development, and that methylation is a consequence rather than a cause of transcriptional regulation.

The art teaches that with respect to acetylation, a similar complex story exists. Similar to Walsh *et al.*, Keohane *et al.* (Dev Biol, 1996) teach that acetylation is associated with X-inactivation in cells, however the role for acetylation is very complex, and conclude that global deactylation in X may be more important for stabilization and maintenance of the inactive state than initiation (page 628, second column) which would be contrary to the instantly claimed methods. In another example of the complexity for the consequence of actylation, Eickhoff *et al.* (Biol Chem, 2000) teach that trichostatin A treatment of cells alters gene expression, however it sensitizes and induces the cell to undergo apoptosis (page 1127), not dedifferentiation. Hou *et al.* (Exp Cell Res, 2002) teach that trichostatin A treatment of human cells in culture reduces telomerase expression and activity in the cells. Telomerase activity is considered a hallmark gene for a undifferentiated cell and a requirement for sustained proliferation of a cell. In light of the teaching in the art that reprogramming a cell is a complex process and the evidence that the

specific agents contemplated in the instantly claimed method clearly do not result in a pluripotent cell, it is found that the specification provides insufficient guidance to practice the method as instantly claimed. Without the necessary guidance in the specification and the lack of correlative working examples, the claims would require an undue amount of experimentation without a predictable degree of success on the part of the skilled artisan.

The instant invention, as claimed, falls under the "germ of an idea" concept defined by the CAFC. The court has stated that "patent protection is granted in return for an enabling disclosure, not for vague intimations of general ideas that may or may be workable". The court continues to say that "tossing out the mere germ of an idea does not constitute an enabling disclosure" and that "the specification, not knowledge in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement". (See *Genentech inc v. Novo Nordisk A/S* 42 USPQ2d 1001, at 1005). The claimed methods of transfer constitute such a "germ of an idea".

In view of the lack of guidance, working examples, breadth of the claims, the level of skill in the art and state of the art at the time of the claimed invention was made, it would have required undue experimentation to make and/or use the invention as claimed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-9 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically:

Claim 1 is vague and incomplete because it is unclear how simply treating a cell with an agent which promotes cellular reprogramming will result in the intended use in the preamble. The claim is incomplete because while cellular reprogramming is an inherent property of the agent, there is no link between the reprogramming and the alteration of a somatic cell to a pluripotent cell. Dependent claims are included in the basis of the rejection because they fail to further clarify the basis of the rejection, only reciting specific agents or cells to be affected.

Claim 4 is unclear and confusing in the recitation of "further comprising treating said adult somatic cell" because while adult somatic cell has antecedent basis in claim 1, the method of claim 1 should result in pluripotent cells, therefore there should be no somatic cells which to further treat. Additionally, it is noted that claim 1 while using open language recites only treating with a single agent. It is unclear if the claim is drawn to an additional step or if the claim is only further limiting the agents set forth in claim 3. If the claim is only further limiting, it is noted that Tat-cyclin B would be considered a new embodiment not encompassed by claim 3 because it is not a cyclin and would not be further limiting.

Claim 9 is unclear and confusing because it recites no further method step so it is unclear how the limitation further limits claim 1. It is unclear if further methods steps are practiced in

claim 9, or if these limitations are inherent to practicing claim 1, and thus, claim 9 is not further limiting.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-4 and 9 are rejected under 35 U.S.C. 102(b) as being anticipated by Yoshihiko *et al.* (1999, IDS reference BB).

Claims 1-4 recite one method step of delivering an agent to a cell as the method is drawn to promoting cellular reprogramming for producing a human pluripotent cell from a somatic cell. Dependent claims recite more specific agents such as an agent which promotes demethylation (claim 2) such as the compound 5-aza-2'-deoxycytidine (claims 3 and 4). The claims can fairly be interpreted to encompass only practicing the specific step recited in the method claims because practicing the method would inherently result the intended use set forth in the preamble. In the instant case, Yoshihiko *et al.* teach a method of culturing cells in the presences of 5-aza-2'-deoxycytidine (see summary in abstract and specific methods on page 37242, bottom of first column). Yoshihiko *et al.* teach that culturing a variety of human cells in the presences of 5-aza-

2'-deoxycytidine alters the methylation of the CpG island of the ABO gene and alters the expression driven from said promoter (see first section in methods for human cells used, page 37241 and results in figure 4, page 37245). It is noted that Yoshihiko *et al.* teach specifically that demethylation can reprogram the expression pattern of the ABO gene, and does not specifically teach that the method of culturing cells in the presences of 5-aza-2'-deoxycytidine results in reprogramming the cell to a pluripotent cell. However, because Yoshihiko *et al.* teach exactly the same method of culturing cells in the presences of 5-aza-2'-deoxycytidine as set forth in the claims, any effect on the cells for these culturing conditions would be inherent to these methods. Therefore, the methods of culturing cells in the presences of 5-aza-2'-deoxycytidine taught by Yoshihiko *et al.* anticipates the claims.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Lenoir-Voiale *et al.* Dermatology Research 285:197-204 (1993) teaches the affect of retinoic acid on outer root sheath cells in culture.

You *et al.* BBRC 28:268-274 (2000) teaches the effect of retinoic acid on keratinocytes in culture.

Each of the above references provide a detailed analysis of cells treated by methods which are similar to those presented in the working examples in the instant specification.

Conclusion

No claim is allowed. Claims 5-8 are free of the art of record because the art does not specifically teach to treat keratinocytes with the agents encompassed by the claims, however they are subject to other rejections.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph Woitach whose telephone number is (703)305-3732.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached at (703)305-4051.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group analyst Dianiece Jacobs whose telephone number is (703) 308-2141.

Papers related to this application may be submitted by facsimile transmission. Papers should be faxed via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center numbers are (703)308-4242 and (703)305-3014.

Joseph T. Woitach

RAM R. SHUKLA, PH.D
PATENT EXAMINER